Mucosal Immune Responses to Microbiota in the Development of Autoimmune Disease

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KEYWORDS

• Microbiota • Pathogenesis • Mucosal immunity • Autoimmune disease

KEY POINTS

- Mucosal microbiota can generate autoimmunity through a variety of mechanisms, including molecular mimicry, alteration of host antigens, exposure of self-antigens, bystander activation, modulation of immune reactivity, and breach of the mucosal firewall.
- Autoimmune disease may be triggered by a single microorganism or alterations of the host microbial community.
- Microbiota changes associated with autoimmune disease may represent causality or a change to the mucosal environment associated with systemic inflammation.
- Prospective studies that evaluate microbial changes at each mucosal site during the preclinical period of autoimmunity are needed to better understand the influence of microorganisms in the pathogenesis of autoimmune disease.
- If specific microbiota are found causal or protective in the development of autoimmune disease, novel strategies can be developed that may ultimately prevent disease.

INTRODUCTION

Humans live in symbiosis with greater than or equal to 10^{14} microorganisms that reside on epithelial surfaces of the body, including the skin and mucosal surfaces of the respiratory, gastrointestinal (GI), and genitourinary (GU) tracts.[1] These microbiota can be pathogenic or nonpathogenic, and they include a diverse community of

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bacteria, viruses, and fungi. The symbiotic nature of the host-microbial relationship implies a mutual benefit. Microbes gain access to habitats and nutrients important for their survival. Humans need microbes for certain metabolic functions as well as proper immune system development and maintenance.

Healthy individuals maintain a well-balanced microbial composition. Although the exact composition of a normal healthy microbiota is currently undefined, it is the focus of the National Institutes of Health–sponsored Human Microbiome Project.[2] Of particular interest for this review, alterations of what may be considered normal healthy microbiota may result in inflammation and autoimmunity, termed *dysbiosis*.[3] Such an imbalance may include an overgrowth or elimination of a single microbial species or changes in the relative abundance (increase or decrease) of multiple microorganisms within the community as a whole. Over the past decade, rapid advances in DNA sequencing technologies have allowed expanding knowledge of this intricate relationship and its potential association with disease. This article reviews data supporting the role of mucosal microbiota in the development of autoimmune disease.

OVERVIEW OF MUCOSAL IMMUNITY

The mucosal immune system (**Fig. 1**) evolved to prevent invasion of resident and pathogenic microbes. The first line of defense is the physical barrier established by a mucus layer overlying epithelial cells. The epithelial layer is typically composed of several cell types, depending on anatomic location. Within the epithelial layer, there are secretory cells that synthesize and secrete proteoglycans to generate mucus as well as other cells that aid in microbial defense. Almost all epithelial cells produce antimicrobial proteins that are retained in the mucus layer.[4] The GI tract, skin, and lung epithelial layers also contain intraepithelial lymphocytes (IELs) that participate in microbial defense (reviewed in Refs.[5,6]). IELs are a heterogeneous group of antigen-experienced T cells that function to protect from microbial invasion and maintain epithelial homeostasis,[7] and similar cells may also be present at other mucosal sites. Not only do the cells of the epithelial layer participate in direct microbial defense but also they aid in communication with other members of the mucosal immune system through cytokine and chemokine production.

Just beneath the epithelial layer is a network of innate immune cells primed for antigen exposure.[8] If microorganisms do breach the epithelial barrier, they are quickly phagocytosed by macrophages; macrophage activation leads to neutrophil, B-cell, and T-cell recruitment. Furthermore, tissue-resident macrophages and dendritic cells continually sample mucosal antigens in the lung and GI lamina propria and migrate to the mediastinal and mesenteric lymph nodes, respectively. Many of these innate cells do not circulate systemically and, therefore, compartmentalize immune responses to the mucosal system. These mucosal draining lymph nodes thus act as a firewall, which allows the host to continuously sample and respond to mucosal microbiota without generating a systemic inflammatory response.[9]

In mucosal lymph nodes, antigen-loaded dendritic cells induce specific IgA^+ B cells to differentiate into plasma cells.[8] The plasma cells then migrate back to the mucosal lamina propria and produce IgA that is transcytosed across the epithelial barrier. IgD antibodies can also be generated and secreted in response to bacteria, specifically the nasal and respiratory mucosa.[10] These mucosal IgD antibodies are often polyreactive in response to bacteria and, of interest, can frequently be autoreactive. Also, within the draining lymph nodes of mucosal sites, T cells are activated and differentiate into one of several subtypes, in particular T-regulatory (Treg) and Th17 T-cell